THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 45

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte BIOCYTE CORP.

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Appeal No. 96-2079
Reexamination Control No. 90/003,182[1]

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HEARD: February 2, 1998

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Before WILLIAM F. SMITH, GRON, and WEIMAR, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

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1 Reexamination proceeding requested August 30, 1993, of Patent No. 5,004,681, issued April 2, 1991, based on Application 07/119,746, filed November 12, 1987, to Boyse et al., entitled "Preservation of Fetal and Neonatal Hematopoletic Stem and Progenitor Cells of the Blood."

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 306 from the final rejection of claims 1 through 12 , all the claims pending in this reexamination of U.S. Patent No. 5,004,681 ('681 patent). Claims 1 through 9 are the original claims of the '681 patent, of which claims 2 through 4, 6, and 8 have been amended. Claims 10 through 12 were added during this proceeding. The claims read as follows:

1. A composition comprising:

(a) a plurality of viable human neonatal or fetal hematopoietic stem cells derived from the blood; and
(b) cryopreservative.

2. The composition of claim 1 which further comprises viable human neonatal or fetal hematopoietic progenitor cells.

3. The composition of claim 1 which further comprises whole neonatal or fetal blood.

4. The composition of claim 1 which further comprises an anticoagulant.

5. The composition of claim 1, 2, 3 or 4 in which the cryopreservative comprises dimethyl sulfoxide.

6. The composition of claim 1 in which the hematopoietic stem cell is characterized by the ability to produce a progeny cell which can produce a colony of granulocyte, erythroid, monocyte, or macrophage progeny in vitro.

7. The composition of claim 2 in which the progenitor cell is characterized by the ability to produce a colony of granulocyte, erythroid, monocyte, or macrophage progeny in vitro.

8. The composition of claim 1 in which the hematopoietic stem cell is characterized by the ability to seed to a spleen and produce a colony of progeny cells, upon introduction into a mammal.

9. The composition of claim 1 in which the hematopoietic stem cell is characterized by the ability to reconstitute the hematopoietic system of a host into which it is introduced.

10. The composition of claim 1 in which the stem cells are from the umbilical cord blood or placental blood of a single human collected at birth of said human.

11. The composition of claim 3 in which the stem cells are from the umbilical cord blood or placental blood of a single human collected at birth of said human, and the whole neonatal or fetal blood is said umbilical cord blood or placental blood of said human collected at birth of said human.

12. The composition of claim 9 in which the stem cells are from the umbilical cord blood or placental blood of a single human collected at birth of said human.

The references relied upon by the examiner are:

Sato et al. (Sato)	4,812,310	Mar. 14, 1989 (Filed Aug. 24, 1987)

Ende et al. (Ende), “Hematopoietic Transplantation by Means of Fetal (Cord) Blood,” Virginia Medical Monthly, Vol. 99, pp. 276-280 (Mar. 1972)

Löwenberg, Fetal Liver Cell Transplantation, Role and Nature of the Fetal Haemopoietic Stem Cell, Chapter 1, Sections 1.3.6 and 2.8, pp. 25-28 and 36 (1975)

Moretti et al. (Moretti), "Cryopreservation of Human Fetal Liver: Factors Influencing Granulocyte-Macrophage Colony (CFU-GM) Survival After Cryopreservation," Fetal Liver Transplantation, pp. 121-133, copyright Alan R. Liss, Inc. (1985)

Shope et al. (Shope), "Epstein-Barr Virus Infection of Cryopreserved Umbilical Cord Blood Lymphocytes," Proceedings of the Society for Experimental Biology and Medicine, Vol. 157, pp. 326-329 (1978)

Valeri, C.R., Blood Banking and the Use of Frozen Blood Products, Chapter 1, pp. 1-7, CRC Press Inc. (1976)

The patent and publications discussed by this merits panel are:

Civin	4,714,680	Dec. 22, 1987 (Filed Feb. 6, 1984)

Broxmeyer (Broxmeyer 1984), "Colony Assays of Hematopoietic Progenitor Cells and Correlations to Clinical Situations," Critical Reviews™ in Oncology/Hematology, Vol. 1, no. 3, pp. 227-57 (1984)

Broxmeyer et al. (Broxmeyer 1989), "Human Umbilical Cord Blood as a Potential Source of Transplantable Hematopoietic Stem/Progenitor Cells," Proc. Natl. Acad. Sci. USA, Vol. 86, pp. 3828-32, (May 1989)

Broxmeyer et al. (Broxmeyer 1991), "Umbilical Cord Blood Hematopoietic Stem and Repopulating Cells in Human Clinical Transplantation," Blood Cells, Vol. 17, pp. 313-29 (1991)

Golde, D. W., "The Stem Cell," Scientific American, pp. 86-93 (Dec. 1991)

Hassan et al. (Hassan), "In Vitro Culture of Erythroid Colonies from Human Fetal Liver and Umbilical Cord Blood, Journal of Hematology, Vol. 41, pp. 477-484 (1979)

Knudtzon, “In Vitro Growth of Granulocytic Colonies From Circulating Cells in Human Cord Blood, Blood, Vol. 43, no. 3, pp. 357-361 (March 1974)

Koike, “Cryopreservation of Pluripotent and Committed Hemopoietic Progenitor Cells from Human Bone Marrow and Cord Blood,” Acta. Paediatr., Vol. 25, no. 3, pp. 275-283 (Sep. 1983)

Koizumi et al. (Koizumi), “Expression of Ia-Like Antigens Defined by Monoclonal OKIal Antibody on Hemopoietic Progenitor Cells in Cord Blood: A Comparison With Human Bone Marrow,” Blood, Vol. 60, no. 4, pp 1046-1049 (Oct. 1982)

Leary et al. (Leary), “Single Cell Origin of Multilineage Colonies in Culture,” J. Clin. Invest., Vol. 74, pp. 2193-2197 (Dec. 1984)

Linch et al. (Linch), Studies of Circulating Hemopoietic Progenitor Cells in Human Fetal Blood,” Blood, Vol. 59, no. 5, pp. 976-979 (May 1982)

Nakahata et al. (Nakahata (J. Clin. Invest.)), “Hemopoietic Colony-forming Cells in Umbilical Cord Blood with Extensive Capability to Generate Mono- and Multipotential Hemopoietic Progenitors,” J. Clin. Invest., Vol. 70, pp. 1324-1328 (Dec. 1982)

Ogawa et al. (Ogawa), “Suspension Culture of Human Mast Cells/Basophils from Umbilical Cord Blood Mononuclear Cells,” Proc. Natl. Acad. Sci. USA, Vol. 80, pp. 4494-4498 (July 1983)

Prindull et al. (Prindull 1975), “Cells in Spontaneous DNA Synthesis in Cord Blood of Premature and Full-term Newborn Infants,” Journal of Pediatrics, Vol. 86, no. 5, pp. 773-778 (May 1975)

Prindull et al. (Prindull 1978), “Haematopoietic Stem Cells (CFU_c) in Human Cord Blood,” Acta Paediatr Scan. Vol. 67, pp. 413-416 (1978)

Prindull et al. (Prindull 1987), “CFU-F Circulating in Cord Blood,” Blut, Vol. 54, pp. 351-359 (1987)

Radvany et al. (Radvany), "Factors Responsible for Successful HLA-DR Typing of Mononuclear Cells From Cord Blood," Tissue Antigens, Vol. 24, pp. 265-269 (1984)

Salahuddin et al. (Salahuddin), "Long-Term Suspension Cultures of Human Cord Blood Myeloid Cells," Blood, Vol. 58, no. 5, pp. 931-938 (Nov. 1981)

Smith et al. (Smith), "The Influence of Oxygen Tension on the Long-Term Growth in Vitro of Haematopoietic Progenitor Cells From Human Cord Blood," British Journal of Haematology, Vol. 63, pp. 29-34 (1986)

Ueno et al. (Ueno), "Characterization of Hemopoietic Stem Cells (CFU_c) in Cord Blood," Exp. Hematol., Vol. 9, no. 7, pp. 716-722 (Aug. 1981)

Vainchenker et al. (Vainchenker), "Growth of Human Megakaryocyte Colonies in Culture from Fetal, Neonatal, and Adult Peripheral Blood Cells: Ultrastructural Analysis," Blood Cells, Vol. 5, pp. 25-42 (1979)

Vidal, "Nature and Characteristics of Granulocyte-Macrophage Precursors in Cord Blood," Thesis, University of Valencia, School of Medicine (1985)

Williams et al. (Williams), "Characterization of Hematoipoietic Stem and Progenitor Cells," Immunol. Res., Vol. 6, pp. 294-304 (1987)

The claims stand rejected as follows:

I. Claims 1 through 12 under 35 U.S.C. § 103 as unpatentable over Shope,
II. Claims 1 through 3 and 5 through 12 under 35 U.S.C. § 103 as unpatentable over Lowenburg or Moretti taken with Ende, and
III. Claims 4 and 5 under 35 U.S.C. § 103 as unpatentable over Löwenberg or Moretti taken with Ende and further in view of Sato or Valeri.

We vacate the examiner's rejections and remand the reexamination to the jurisdiction of the examiner to consider the issues raised below and to take appropriate action.

BACKGROUND

1. Stem/progenitor cells

The claims of the '681 patent are directed to compositions which comprise a plurality of viable human neonatal or fetal hematopoietic stem cells derived from the blood in combination with a cryopreservative. As explained in Williams (1987)[2] (page 294, opening paragraph):

> Hematopoiesis in the adult mammal involves the proliferation and differentiation of primitive, morphologically unrecognizable cells within the hematopoietic organs to supply mature blood cells. The relatively short life-span of mature myeloid cells necessitates a continuous efflux of cells from the primitive cell pool into the maturing cell pool.
>
> * * *
>
> The primitive hematopoietic cells giving rise to morphologically recognizable blood cells can be divided into two major subtypes: stem cells and progenitor cells.

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[2] This reference is co-authored by co-inventor Broxmeyer. The precise day in 1987 on which Williams was published is not clear. Regardless of whether it was published before or after the November 12, 1987, filing date of the '681 patent, it is relevant in establishing how co-inventor Broxmeyer and persons skilled in the art viewed the technical subject matter under review in this appeal. See In re Baxter Travenol Labs., 952 F.2d 388, 390, 21 USPQ2d 1281, 1284 (Fed. Cir. 1991).

Figure 1 of Williams schematically depicts the hierarchy of the hematopoietic cell lines as follows:

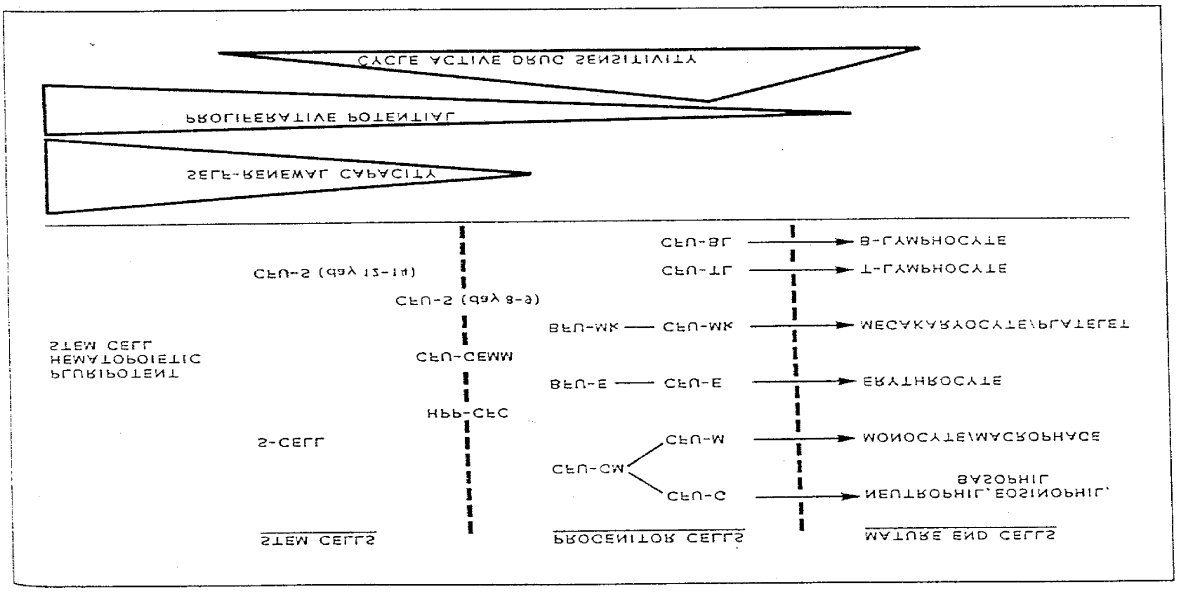

Fig. 1. A schematic representation of one current view of the hematopoietic stem cell hierarchy. Three major classes of cells make up the hierarchy: stem cells, progenitor cells, and morphologically recognizable cells. Stem cells possess self-renewal potential and extensive proliferative potential but only minimal sensitivity to cycle active drugs since they are not actively cycling in the steady state. Progenitor cells have lost all or most of their self-renewal capacity, retain some proliferative potential and are most sensitive to cycle-specific drugs since a high proportion of them are actively cycling. S-cell = in vitro stem cell; HPP-CFC = high proliferative potential megakaryocyte (M) colony-forming cell; BFU-E = erythroid burst-forming unit; CFU-E = erythroid colony-forming cell; BFU-MK = megakaryocyte burst-forming unit; CFU-MK = megakaryocyte colony-forming cell; CFU-TL = T-lymphocyte colony-forming cell; CFU-BL = B-lymphocyte colony-forming cell.

The specification of the ‘681 patent is in agreement with this view of the hematopoietic system and further notes that “The definitions of stem and progenitor cells are operational and depend on function, rather than on morphological criteria.” See column 1, lines 4-39.

Three stem cells are identified in Figure 1 of Williams (1987), pluripotent hematopoietic stem cell (PHSC), S-cell and CFU-S. Williams (1987) teaches that PHSC is the most primitive cell in the hematopoietic system and gives rise to cells of both the lymphoid and myeloid series and provides long-term repopulation of the hematopoietic organs following bone marrow transplant. See page 294, right hand column. As explained on pages 295-96 of Williams (1987), functional assays have been described in the prior art which quantitate cells which possess self-renewal capability and extensive proliferative capacity. These cells are termed CFU-S. As to the third type of stem cell, Williams (1987) acknowledges that Nakahata (J. Clin. Invest.) described an in vitro assay which identifies the S-cell. See the paragraph bridging the columns on page 296. Williams (1987) states at the end of that paragraph that since there was no available evidence yet concerning the possible lymphoid differentiation potential of the S-cell, the relationship between the PHSC and the S-cell is unclear. However, Williams (1987) concludes that the S-cell is one of the most primitive cell types which can be grown in vitro and it does possess some of the features of the PHSC.

The discussion in the specification of the ‘681 patent regarding stem cells and progenitor cells is consistent with the discussion of these cells in Williams (1987). See column 3, line 40--column 4, line 14. Of special significance is the acknowledgment in the specification of the ‘681 patent at column 12, lines 7-11, that the work of Nakahata (J. Clin. Invest.), which involved human umbilical cord blood, indicated that S-cells represent “probably the earliest developmental form of the stem cell.” In fact, the specification of the ‘681 patent defines the S-cell simply as “stem cell” at column 9, line 29. The specification of the ‘681 patent is also in agreement with Williams (1987) that the CFU-S cell is properly called a stem cell. See column 9, lines 7-10.

While Williams (1987) was published no later than just after the filing date of the ‘681 patent, Broxmeyer (1984) was published prior thereto. This review article is stated to be “an updated and extended overview of previously published reviews to the pluripotential stem cells” (page 227, citations omitted). At page 230 Broxmeyer (1984) states:

> A human progenitor cell with extensive renewal capacity, similar to that described for mouse cells, [citations omitted] has been found in umbilical cord blood [citing Nakahata, (J. Clin. Invest.)] and this cell may be an earlier cell in the hierarchy than CFU-GEMM.

Co-inventor Broxmeyer's view of the hematopoietic system in terms of what constitutes a stem cell continued in a consistent manner after the filing date of the '681 patent. Broxmeyer (1989)[3] acknowledges on page 3828 that:

> Stem/progenitor cells occur in fetal blood [citation of references published in 1982 and 1986], and human umbilical cord blood contains stem cells [citation of Nakahata (J. Clin. Invest.)and Leary], so called because in colony assay in vitro they exhibit replating efficiency indicative of self-renewal, as well as multipotential (CFU-GEMM), erythroid (BFU-E), and granulocyte-macrophage (CFU-GM) progenitor cells [citation of references dated from 1974 to 1986, including, again, Nakahata (J. Clin. Invest. and Leary].

2. Umbilical cord blood and fetal blood

The claims of the '681 patent specify that the plurality of stem cells be derived from human neonatal or fetal blood. Human neonatal blood is typically obtained from umbilical cords or placentas. See the '681 patent, column 12, lines 54-57. The '681 patent indicates at column 12, lines 43-53, that fetal blood can be obtained "by any method known in the art." Umbilical cord and fetal blood had been the subject of research for a variety of reasons for many years prior to the November 12, 1987, filing date of the '681 patent. As set forth in column 4, lines 15-40, of the '681 patent:

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[3] This publication also lists the remaining two co-inventors of the '681 patent as co-authors.

> A human hematopoietic colony-forming cell with the ability to generate progenitors for secondary colonies has been identified in human umbilical cord blood (Nakahata, T. and Ogawa, M., 1982, J. Clin. Invest. 80:1324-1328). In addition, hematopoietic stem cells have been demonstrated in human umbilical cord blood, by colony formation, to occur at a much higher level than that found in the adult (Prindull, G., et al., 1978, Acta Paediatr. Scan. 67:413-416; Knudtzon, S., 1974, Blood 43(3):357-361). The presence of circulating hematopoietic progenitor cells in human fetal blood (Linch, Fauser, A. A. and Messner, H. A., 1978, Blood 52(6):1243-1248) has also been shown. Human fetal and neonatal blood has been reported to contain megakaryocyte and burst erythroblast progenitors (Vainchenker, W., et al., 1979, Blood Cells 5:15-42), with increased numbers of erythroid progenitors in human cord blood or fetal liver relative to adult blood (Hassan, M. W., et al., 1979, Br. J. Haematol. 41:477-484; Tchernia, G., et al., 1971, J. Lab. Clin. Med. 97(3);322-331). Studies have suggested some differences between cord blood and bone marrow cells in the characteristics of CFU-GM (colony forming unit-granulocyte, macrophage) which express surface Ia antigens (Koizumi, S., et al., 1982, Blood 60(4):1046-1049.

For an understanding of the interest researchers have had in studying the properties and uses of fetal or cord blood, both before and after the filing date of the '681 patent, we direct attention to the following documents:

1972

Ende--16 year old leukemic patient transfused multiple times with human umbilical cord blood from multiple donors. Ende reports (page 276) that the patient "apparently developed a successful temporary allograft from a relatively small number of fetal cells."

1974

Knudtzon[4]--Reports finding an increased concentration of hematopoietic progenitor cells in human umbilical cord blood. After determining that the concentration of colony forming units in human cord blood is comparable in number with human bone marrow cultures Knudtzon concluded (page 360) that this "indicates that cord blood might be used as a source of hemopoietic stem cells for the restoration of bone marrow function in humans."

1975

Prindull (1975)--Determined that the number of cells in spontaneous DNA synthesis is higher in cord blood of premature and full-term infants. This finding raised "the question whether [these cells] may be, at least in part, hematopoietic stem cells." (Paragraph bridging pages 776-77). Prindull cites Knudtzon and concludes (page 777, citation omitted) that in view of their own and Knudtzon's findings that "cells in spontaneous DNA synthesis . . . most likely, at least In part, represent hematopoietic stem cells of a particular stage of development."

1978

Shope--Separated whole heparinized human umbilical cord blood using Ficoll-hypaque gradient and cryopreserved the resulting mononuclear fraction using dimethyl sulfoxide (DMSO) as a cryopreservative. Cells in thawed samples were infected and transformed by Epstein-Barr virus (EBV). Shope concluded that this procedure provided a cell storage system which preserved cells in a state comparable to fresh cultures of cells and provided a "convenient time and resource saving advance" (page 329).

Prindull (1978)--Indicates that "Since, in the foetus, the haematopoietic system is in a state of physiologic proliferation, cord blood might constitute another source of haematopoietic stem cells." Plating experiments involving fractions of human cord blood established the presence of CFUc progenitor cells.

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[4] Patent owner admitted at page 4 of the response filed on September 11, 1989, during the prosecution of the '681 patent that Knudtzon discloses the presence of stem cells in human umbilical cord blood.

1979

Hassan--Separated human umbilical cord blood using Ficoll-Paque and cultured the fraction containing mononuclear cells resulting in colonies composed of either mature or immature cells, suggesting the presence of erythroid colony progenitors.

Vainchenker—Obtained blood from human umbilical cords and from a 22-week old aborted fetus. Separated the samples using a procedure which included "Ficoll metriazoate density centrifugation." Mononuclear cells were cultured and megakaryocyte progenitors were observed.

1981

Ueno—Separated whole heparinized human umbilical cord blood using Ficoll-Hypaque gradient. Cultured mononuclear cell fraction and observed progenitor colonies.

Salahuddin-- Separated whole heparinized human umbilical cord blood using Ficoll-Hypaque gradient. Resulting studies indicated that the techniques described therein are useful in the study of myeloid and monocyte cell growth and differentiation.

1982

Nakahata (J. Clin. Invest.)—Cultured mononuclear cells obtained from human umbilical cord blood and obtained CFU-GEMM colonies. Replated individual CFU-GEMM colonies and obtained a large number of secondary colonies, albeit no detection of lymphoid secondary colonies. Concluded that the progenitors which were replated were more primitive than CFU-GEMM, in part, because of the ability to self renew. As set forth above, this reference is cited in the '681 patent as disclosing the "S-cell."

Linch[5]—Studied circulating hematopoietic progenitor cells in human fetal blood obtained by aspiration from an umbilical vessel under fetoscopic control. Concluded that the measured high level of circulating hematopoietic progenitor cells in fetal blood

[5] Patent owner admitted at page 5 of the response submitted September 11, 1989, during the prosecution of the '681 patent that Linch suggests the presence of stem cells in fetal blood.

supported the concept that developing bone marrow is colonized by circulating stem cells (Right hand paragraph, page 978).

Koizumi--Separated whole heparinized human umbilical cord blood using Ficoll-Hypaque gradient. Cultured the resulting mononuclear cell fraction and characterized the surface antigen structure of the resulting progenitor cell colonies.

1983

Ogawa--Separated whole heparinized human umbilical cord blood using Ficoll-Hypaque gradient. The resulting mononuclear cell fraction was cultured and the resulting mast cells and basophils were recovered. Ogawa then determined that such highly enriched human mast cell/basophil cultures “will provide useful tools for characterization of IgE receptors and for biochemical analysis of mediator release.” (concluding paragraph).

Koike-- Separated whole heparinized human umbilical cord blood using Ficoll-Hypaque gradient. A portion of the mononuclear cell fraction was immediately cultured for progenitor cell assay and the rest cryopreserved using DMSO. After 1-5 months cryopreserved cells were thawed and cultured in the same manner as the fresh sample. Results of recovery of mononuclear cells, CFU-GM, CFU-E, BFU-E and CFU-mix, from cryopreserved cord blood were compared with values from cryopreserved bone marrow. Results indicated that the more immature CFU-mix and primitive BFU-E were viable and proliferated after cryopreservation. Koike concludes (final paragraph): “the results that cord blood cells contain many pluripotent and nearby progenitor cells comparable to marrow cells, indicate that fetal hemopoietic cells or organs may be useful as one of the sources of hemopoietic progenitor cells for marrow transplantation.”

1984

Radvany—HLA-DR typed mononuclear cells from fresh samples, older samples and cryopreserved samples of human umbilical cord blood. Cord blood samples were collected in heparin and separated using the “ficoll flotation” method. Fresh samples were analyzed within 12h of collection. Older samples were preserved for 12-48h at 22^{o}C before being analyzed. The cryopreserved samples were frozen in liquid nitrogen using DMSO as a cryopreservative. Ten of the eleven freshly frozen samples were successfully DR typed.

Leary—Reports analysis of differentiation in human hemopoietic colonies derived from a single cell. Mononuclear cells obtained from human umbilical cord blood using Ficoll-Paque were cultured. An additional cord blood sample was enriched for progenitors by panning with monoclonal antibody anti-My-10 and cultured. Single cells were separated from the resulting colonies obtained from both the Ficoll fraction and the enriched sample using a micromanipulator and replated. Colonies obtained from replated single cells included single lineage and mixed lineage hemopoietic colonies. As reported on page 2194, the "highest incidence of colony formation was observed when 32 single cells were replated from cultures of My-10-positive umbilical cord mononuclear cells."

Civin[6]—Describes the discovery of an antigen designated My-10 that is expressed on pluripotent lymphoid-hematopoietic stem cells (stem cells). Civin indicates (column 3, line 67-column 4, line 2) that "The ability to detect My-10 antigen diminishes rapidly as blast cells differentiate into mature myeloid and lymphoid cells." As set forth on column 4, line 49-52, "Anti-My-10-positive antibodies are extremely useful in hematopoietic research because ant-My-10 antibodies label the lympho-hematopoietic progenitor cell subset more specifically that [sic] any previously described antibody." Of special significance is the disclosure at column 5, lines 4-7, that "Anti-My-10 antibody is unique in that it recognizes an antigen on the progenitor cells CFC-GM, BFU-E, CFC-Eo, and GFC-GEMM, but does not recognize an antigen on mature, human myeloid or lymphoid cells."

In the paragraph bridging columns 7-8, Civin states:

> The above methods of treating marrow or blood cell suspensions produce a suspension of human cells that contains pluripotent lympho-hematopoietic stem cells, but substantially free of mature lymphoid and myeloid cells. The cell suspension also contains substantially only cells that express the My-10 antigen and can restore the production of lymphoid and hematopoietic cells to a human patient that has lost the ability to produce such cells because of, for example, radiation treatment. By definition, a cell population that can

[6] Civin is available as prior art under 35 U.S.C. § 102(e) as of its February 6, 1984, filing date.

> restore the production of hematopoietic and lymphoid cells contains pluripotent lympho-hematopoietic stem cells.

Civin also teaches at column 7, lines 38-42, that the enriched fraction of cells may be cryopreserved in a viable state for later use.

1985

Vidal thesis[7]—Discusses the nature and characteristics of human umbilical cord blood. One of the purposes of the research set forth in the thesis is "To find possible clinical uses for cord blood." (translation, page 17). Vidal separated heparinized human cord blood using Ficoll-Paque (translation, page 17). The mononuclear cell fraction was cultured and growth of CFU-GM colonies was observed. Importantly, the following conclusions are reached by Vidal (translation, page 101):

1. "Knowing the high concentration in cord blood not only of CFU-GMs but also of CFU-GEMMs and even more ancestral cells [citation of Nakahata (J. Clin. Invest.)], we might consider the use thereof as source of precursors for hematopoietic transplants."

2. The only limitation might be the approximate volume of blood ÿ [but] [t]his limitation would exist only for adults since a new born infant of normal weight would receive the optimal dose."

3. "If we furthermore take the immuno-tolerance of the new born child into account, we see that there are even possibilities of using non-identical HLA donors."

Finally, Vidal concludes (translation, page 102):

> My hypothesis is that since cord blood contains sufficient hematopoietic stem cells to effect a transplant, cord blood can be used for this purpose in

[7] The original document is in the Spanish language. Our consideration of the reference has been based upon the record copy of the English language translation thereof.

> fatal genetic diseases, which can be diagnosed intrauterinely and with it program the intervention and locate a donor having certain similar HLA antigens. Furthermore, cryopreserved cord blood banks might exist.

1986

Smith—This paper is co-authored by co-inventor Broxmeyer. Smith indicates on page 29 that "The long-term production of haematopoietic progenitor cells is important experimentally and clinically." Fresh, heparinized cord blood was separated using Ficoll-Hypaque and the resulting interface low density cells were set up for long term culture.

1987

Prindull (1987)—This paper was published after the filing date of the '681 patent. It is of interest for its statement at page 351 that: "The hemato-lymphopoietic system of the neonate is in a state of physiologic proliferation. This activity is reflected in the fetal circulation by the presence of immature leukocytes including hematopoietic stem cells [citation of two references published in 1974 and 1978 omitted]."

1991

Golde--This review discusses the different components of the human hematopoietic system, emphasizing the stem cell. In discussing stem cells Golde states (page 86) that:

> Stem cells have varying degrees of 'stemness,'. . . The most fundamental cell in this family is the so-called totipotent stem cell; in principle, a single totipotent stem cell can permanently reconstitute the entire blood-producing and immune systems. Stem cells that are less general but that can still differentiate into several lines are called pluripotent.

Golde also states at page 92 that:

> Workers have known for nearly two decades that cord blood contains blood cells progenitors. Using his stem cell colonies, Ogawa showed in 1987 that umbilical cord blood contains pluripotent stem cells. [Present co-inventors Boyse and Broxmeyer] and Elaine Gluckman . . . , conceived of using cord blood for transplantation.

Broxmeyer (1991)--This paper, co-authored by co-inventors Boyse and Broxmeyer, discusses the present invention stating:

> More than 7 years ago, in a meeting set up by Dr. Edward A. Boyse, he and Dr. Hal E. Broxmeyer discussed the possibilities of using the usually discarded umbilical cord blood. After a description of the above-mentioned in vitro stem/cell progenitor cells found in cord blood, Boyse made the suggestion that human umbilical cord blood might be a clinically useful source of transplantable hematopoietic repopulating cells.

3. The ‘681 patent

In understanding the issues presented in this appeal it is important to keep in mind that the claims on appeal are directed to compositions, not methods of use. Thus, while the compositions described in the ‘681 patent are intended to be used for the purpose of hematopoietic reconstitution, it is the patentability of the claimed compositions which is in issue in this appeal.[8]

The ‘681 patent prefers to use compositions which comprise whole cord blood. See, e.g., column 18, lines 27-30:

> In a preferred embodiment of the invention, whole neonatal blood, as collected, can be cryogenically frozen, thus minimizing cell losses which can be incurred during cell processing protocols.

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[8] Patent owner subsequently obtained U.S. Patent No. 5,192,553 which contains claims to methods of hematopoietic reconstitution of humans. This patent is stated to be based upon a continuation-in-part application of the application which matured into the ‘681 patent.

The ‘681 patent also describes compositions which comprise fractionated or separated cord blood wherein the separated fraction is optionally enriched in stem and progenitor cells. See column 18, lines 30-35. Separating whole cord blood can lead to loss of hematopoietic stem and progenitor cells. See column 18, lines, 35-40. The ‘681 patent cautions that “if cell separation is desired, care should be taken to ensure sufficient recovery of the hematopoietic stem and progenitor cells.” (column 18, lines 50-53).

The ‘681 patent acknowledges at column 18, line 61-column 19, line 19, “Recently, procedures have been reported for the isolation of very highly enriched populations of stem/progenitor cells.” References dated from 1984-1986 are cited as describing such techniques. Of special significance is the disclosure at column 19, lines 20-37, which reads as follows:

> Human stem and progenitor cells are present in the non-adherent, low density, T-lymphocyte-depleted fraction of bone marrow, spleen, and (adult and cord) blood cells. In a specific embodiment, low density (density less than 1.077 gm/cm^3) cells can be separated by use of Ficoll-Hypaque (Pharmacia Fine Chemicals, Piscataway, N.J.)(see Section 6.3.1, infra) or Percol (Broxmeyer, H. E., 1982, J. Clin. Invest. 69:632-642). In this procedure, the mature cells of the granulocytic series, which are not needed for transplantation, are removed in the dense fraction which goes to the bottom of the tube. An adherence/nonadherence separation protocol can also be used for enrichment of hematopoietic stem and progenitors; protocols which can be used are described in section 6.3.2, infra, and in Broxmeyer, H. E. et al., 1984, J. Clin. Invest. 73:939-953, which is incorporated by reference herein.

The ‘681 patent also acknowledges that stem/progenitor cells contain the My-10 antigen. See column 20, lines 40-52, citing, inter alia, Leary. Leary is also cited at column 21, lines 60-64, in support of the statement that “there are ways to separate hematopoietic stem and progenitor cells from other cord blood cells.”

In discussing cryopreservation in column 22, line 25-column 24, line 16, the ‘681 patent indicates that DMSO is but one known cryopreservative agent which can be used in the compositions of the patent. Among the other cryopreservative agents described by the ‘681 patent is albumin. See column 22, line 46. As indicated above, it is only preferred in the ‘681 patent that whole neonatal blood be cryopreserved and thawed prior to use. See column 24, lines 33-35. The working examples of the ‘681 patent, which involved mouse studies, used fresh, whole non-cryopreserved murine fetal blood. See column 53, line 50-column 56, line 60.

As previously indicated, the definition of stem cell in the ‘681 patent includes the S-cell of Nakahata (J. Clin. Invest.). As explained at column 48, lines 38-54, of the ‘681 patent:

> The assay used for stem cell (S-cell) quantitation does not directly assay self-renewal, but instead assays for the ability to generate secondary multilineage colonies on replating. This assay is done essentially the same as the BFU-E/CFU-GEMM assays, except that cultures are scored after 21-

> 28 days of incubation rather than after 14 days (for BFU-E and CFU-GEMM). The drug 4-hydroperoxycyclo-phosphamide (4HC) appears to spare immature progenitors at the expense of mature progenitors, and may be useful for pretreating cells before assay. Factors which can be tested for increasing assay efficiency) include but are not limited to hemin, oxygen tension (Smith, S. and Broxmeyer, H. E., 1986, Brit. J. Haematol. 63:29-34), superoxide dismutase, glucose oxidase, IL-3, GM-CSF, C-CSF, M-CSF, erythropoietin, IL-1, IL-4, etc.

It is important to understand that the results set forth in Table III of the '681 patent were obtained from progenitor cell assays which did not involve the replating step of Nakahata (J. Clin. Invest.) and, thus, are not necessarily indicative of the presence of the S-cell. This is confirmed at column 48, lines 38-44, where the '681 patent reiterates that a replating step is needed in order to assess the self-renewal properties of the cells grown in primary cultures. In other words, none of the separated samples tested in Table III of the '681 patent were shown to contain PHSCs, S-cells or CFU-Cs.

4 Reexamination history

The request for reexamination of the '681 patent was filed on August 30, 1993, on behalf of third party requester Cryo-Cell International, Inc.. The request set forth numerous reasons why the cited references raised substantial new issues of patentability. The examiner agreed and issued an order granting the request for reexamination on November 5, 1993. The order included ten proposed rejections of the claims of the '681 patent.

Patent owner filed a statement under 35 U.S.C. § 1.530 on February 4, 1994, which discussed the proposed rejections. Accompanying the statement were declarations under 37 CFR § 1.132 by Dr. Irwin D. Bernstein (Bernstein I) and co-inventor, Dr. Hal E. Broxmeyer (Broxmeyer I). In discussing the proposed rejections under 35 U.S.C. § 103, patent owner took the position that the cited references must establish "a reasonable expectation that human neonatal/fetal blood contains hemopoietic stem cells that have therapeutic utility for the reconstitution/repopulation of the human blood/immune system." (Paper No. 9, page 26). Patent owner then defined the phrase "hematopoietic reconstitution" as meaning "long term" hematopoietic reconstitution in contrast to blood replacement which is routinely effected by blood transfusion, id. , citing Bernstein I, paras. 8 and 17 in support. Paragraph 8 of Bernstein I reads as follows:

> 8. Stem cells are the most primitive cells in the hematopoietic lineage; they have extensive self-renewal capacity and the ability to differentiate into progenitor cells. The true human hematopoietic stem cell is the cell with long-term multilineage marrow repopulating ability, although other cells have been loosely termed stem cells, such as those detected by the CFU-s (spleen colony forming) assay or the ability to give rise to in vitro blast cell colonies that can be replated in vitro to form secondary colonies containing the different mature blood cell types. Thus, I will employ the term "stem cell" herein in this broader sense. It is the stem cell with long-term marrow repopulating ability that, in sufficient amounts, has utility for long-term (multilineage) hematopoietic reconstitution. Bone marrow transplantation, for example, is done to effect long-term hematopoietic reconstitution, and is often attempted using cryopreserved bone marrow. As is clear from the

> context in which it is used, the term "hematopoietic reconstitution" is used in the '681 Patent to mean "long-term" hematopoietic reconstitution.

Thus, Dr. Bernstein considers the PHSC, CFU-s, and S-cell to be "stem cells."

The examiner issued a first Office action on May 20, 1994, (Paper No. 11) in which 11 rejections were made. Nakahata (J. Clin. Invest.) was used in support of rejections under 35 U.S.C. § 103 for its disclosure that "human hematopoietic stem cells may be obtained from umbilical cord blood." (Paper No. 11, page 13). In addition, claims were rejected under 35 U.S.C. § 103 on the basis of Shope alone (Paper No. 11, pages 13-14). Claims were also rejected under 35 U.S.C. § 103, inter alia, on the basis of Löwenberg, Moretti and Ende (Paper No. 11, pages 9-11).

Patent owner responded to the first Office action on July 20 1994, (Paper No. 14). In arguing the rejection based on Shope alone, patent owner cast the issue into one of "inherency" (Paper No. 14, pages 19-54). Reliance was placed on second declarations filed under 37 CFR § 1.132 by Drs. Bernstein and Broxmeyer (Bernstein II and Broxmeyer II, respectively). In presenting arguments in response to this rejection, patent owner did not address any single claim. Nor did Dr. Bernstein or Dr. Broxmeyer address any single claim in their declarations.

In responding to the rejection which involved Ende (Paper No. 14, pages, 69-72), patent owner argued that Ende only observed "a brief, temporary change in the patient's red blood cell (erythrocyte, a mature cell) phenotype." Dr. Bernstein agreed with this interpretation of Ende. See paragraph 31 of Bernstein II. In discussing this issue, both patent owner and Dr. Bernstein emphasized that in their view the term "hematopoietic reconstitution" as used in the '681 patent means long-term complete repopulation of the blood components in vivo. See Bernstein II, paragraph 9 and Paper No. 14, page 7.

Patent owner dismissed Nakahata (J. Clin. Invest.) on the basis that it "does not teach the presence of stem cells which afford efficacy in human hematopoietic reconstitution" (Paper No. 14, page 80). Dr. Bernstein agreed with this interpretation of Nakahata (J. Clin. Invest.) (Bernstein II, paragraph 21).

The examiner requested "clarification" of the term "stem cell" in a telephone interview conducted with counsel on August 24, 1994. As set forth in the form PTOL-474, REEXAMINATION INTERVIEW SUMMARY FORM (Paper No. 17):

> Examiner Dadio requested clarification of the term "stem cells" as used in the '681 Patent. Ms. Antler [counsel of record] defined the term as those pluripotential stem cells with long-term marrow repopulating ability as well as other cells such as those pluripotential cells which have self-renewal capacity.

The examiner subsequently dropped reliance upon Nakahata (J. Clin. Invest.) in the final Office action, Paper No. 18, mailed November 1, 1994, stating (page 6) that if the cells of Nakahata (J. Clin. Invest.) were used in the manner proposed by the rejection "the skilled artisan would NOT obtain a composition comprising 'human neonatal or fetal hematopoietic stem cells derived from the blood' as the claims of the '681 Patent require and as the terms are defined in the specification." However, the examiner explicitly disagreed with patent owner's definition of the term "hematopoietic reconstitution," stating at page 2 of the final Office action:

> Patent Owners' [sic] initial response, see for example pages 7-11 and 15-16 of the Response filed July 7, 1994, discusses the definition of the term "hematopoietic reconstitution": which they allege is consistent with the usage in the '681 Patent. Patent Owners state that the term "means 'long-term' complete (multilineage) hematopoietic repopulation in vivo." See Response, page 7. The Examiner disagrees with Patent Owners' [sic] allegation that such definition is consistent with the term used in the '681 patent. The '681 patent does not appear to define or indicate that the term refers to "long-term" repopulation. Moreover, the terminology "long-term" is not clearly defined. It is unclear as to the length of time which may be considered as "long-term".

Furthermore, the examiner stated in the paragraph bridging pages 2-3 of the final Office action that:

> Further, Patent Owners [sic] urge the definition for the term "stem cell" as used in the '681 patent is defined as those pluripotential cells with the "long-

> term marrow repopulating ability" as well as "[c]ells other than the long-term marrow-repopulating" cells. Those "other" cells which are encompassed in the definition of the term "stem cells" are said to be those pluripotential cells that have self-renewal capacity. See, Response, pages 7-8. The original specification as filed in the Patent supports this position and definition, see columns 3 and 4 of Patent. Furthermore, this definition is consistent with the Examiner's telephone interview with Ms. Adriene [sic, Adriane] Antler on Wednesday, August 24th, 1994. See, attached Telephone Interview Summary. Thus, it is recognized that there are more than one type of "stem cell" and applicants intend for the term to be defined in the '681 patent as encompassing this broad definition.

Patent owner disagreed with the examiner's reason for dropping reliance on Nakahata (J. Clin. Invest.), arguing in the response of December 28, 1994, (Paper No. 20, page 14) that "the germane point is that [Nakahata (J. Clin. Invest.)] does not teach that the detected cells are the stem cells that can effect hematopoietic reconstitution." The examiner did not consider patent owner's position on this issue to be persuasive. See the Form PTOL-467 REEXAMINATION ADVISORY ACTION (Paper No. 24, pages 3-5).

Patent owner continued to dispute the examiner's reasoning for dropping reliance on Nakahata (J. Clin. Invest.) in the Appeal Brief. See pages 123-144 of the Appeal Brief. Patent owner argued at page 124 of the Appeal Brief "Nakahata . . . describes cells with the ability to generate progenitors for secondary colonies, and that thus appear to be a type of stem cell as that term is used in the '681 Patent" but that "this ability to generate

progenitors does not indicate the presence of the stem cell with the ability to effect hematopoietic reconstitution."

The examiner maintained her position that "the progenitor cells of [Nakahata (J. Clin. Invest.)] are not a type of stem cells [sic] as that term is used in the '681 Patent" (Examiner's Answer, pages 21-22, emphasis added). However, the examiner went on to state at page 22 of the Examiner's Answer that "If the cells of [Nakahata (J. Clin. Invest.)] are indeed encompassed by the definition of the "stem cells" as used and defined in the '681 Patent, then the rejection may have been incorrectly withdrawn." The examiner did not resolve the issue and did not reinstate a rejection based upon Nakahata.

A second supplemental Information Disclosure Statement (IDS) was filed by patent owner on June 10, 1997, (Paper No. 39) in which Koike and the Vidal thesis were first made of record in this reexamination. In submitting these references, patent owner only indicated that the references had been cited in opposition proceedings, either in the European Patent Office in connection with a European patent related to the '681 patent or in the Japanese Patent Office in connection with an accepted Japanese patent application related to the '681 patent. The second supplemental IDS did not discuss any individual reference in detail.

The second supplemental IDS was considered by an examiner who was newly assigned to this reexamination. This examiner issued a communication on December 3, 1997, (Paper No. 41) stating that "[a]ll of the cited references have been considered by the examiner." The examiner determined that the Vidal thesis was the "most relevant reference" but that "[t]his reference teaches only of the abundance of stem cells in cord blood which is no more than what is taught by the references relied upon in the rejections of claims 1-12 now on appeal." The examiner did not separately discuss Koike.

In pursuing this appeal, patent owner relies upon secondary considerations as evidence of non-obviousness, including long-felt need, skepticism initially expressed by experts and subsequent acceptance and recognition of the invention, copying of the claimed invention by others and unexpected results. See pages 144-225 of the Appeal Brief. Patent owner indicates that the long-felt need fulfilled by the present invention is an "effective, abundant, inexpensive, safely and easily obtainable [composition] for use in hematopoietic reconstitution." (Appeal Brief, page 148). Patent owner relies upon post-issuance publications in support of the asserted skepticism and subsequent acceptance of the present invention. In similar fashion, post-issuance publications are used to support the assertions of copying by others and unexpected or surprising results.

DISCUSSION

A

Consideration of the rejections pending in this appeal is difficult since the prosecution and examination which has occurred in this reexamination to date has not been based on a complete and consistent interpretation of any individual claim. Consideration of the issues raised in this appeal is also difficult since the relevant legal standards which govern these issues have not been identified and applied. These errors have resulted in prior art which is more relevant in determining the patentability of the claims on appeal than is applied in the extant rejections being withdrawn, overlooked or ignored by the examiner and patent owner.

The two references relied upon by the examiner which do involve umbilical cord blood, Shope and Ende, have been considered by the examiner and patent owner in a vacuum, apart from the wealth of knowledge contained in the prior art as to the constituents and properties of umbilical cord blood. The relevance these disclosures may have in determining the patentability of the claims on appeal becomes more apparent when the prior art as a whole and the manner in which the claimed invention is disclosed in the specification of the ‘681 patent are taken into account.

For example, the examiner has rejected claims 1 through 12 under 35 U.S.C. § 103 on the basis of the disclosure of Shope. The examiner made a finding at page 6 of the Examiner's Answer that "The mononuclear cell fraction isolated by Shope necessarily includes large numbers of lymphocytes, monocytes and stem and progenitor cells." The examiner relied upon a declaration filed by Dr. David T. Harris submitted by the third party requestor with the request for reexamination in support of this finding.

Patent owner recast this rejection in the form of a rejection under 35 U.S.C. § 102 as based upon inherency. See, e.g., pages 34-84 of the Appeal Brief. The main point made by patent owner is that a Ficoll-Hypaque separation method as used in Shope to obtain the mononuclear cell fraction which was cryopreserved "does not inevitably result in recovery of viable stem cells." (Appeal Brief, page 12). Reliance was placed on Bernstein I and Broxmeyer I as well as the declaration of Dr. Edward A. Boyse filed December 28, 1994.

Missing, however, in the discussion which has occurred between the examiner and patent owner concerning the effect Shope has on the patentability of the claims on appeal is an analysis of the scope of any individual claim on appeal. For example, claim 1 requires a "plurality of viable human neonatal or fetal hematopoietic stem cells derived

from blood." A dictionary[9] definition (page 1097) of "plurality" is "the condition of being plural or numerous." The word "plural" is defined in this dictionary (page 1096) as meaning "of or including more than one."

Claims in a reexamination are given their broadest reasonable interpretation consistent with the specification. In re Paulsen, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994), citing In re Etter, 756 F.2d 852, 858, 225 USPQ 1, 5 (Fed. Cir. 1985). Our appellate reviewing court put this legal standard in perspective in In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997), where, in discussing the standard to be used in construing or interpreting claims during an ex parte proceeding in the Patent and Trademark Office (PTO), the court stated:

> Some cases state the standard as 'the broadest reasonable interpretation," see e.g., In re Van Geuns, 988 F.2d 1181, 1184, 26 USPQ2d 1057,1059 (Fed. Cir.1993), others include the qualifier 'consistent with the specification' or similar language, see, e.g., In re Bond, 910 F.2d 831, 833, 15 USPQ2d 1566, 1567 (Fed. Cir.1990). Since it would be unreasonable for the PTO to ignore any interpretive guidance afforded by the applicant's written description, either phrasing connotes the same notion: as an initial matter, the PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever

[9] Webster's New World Dictionary, Second College Edition, The World Publishing Company, New York, 1972.

> enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification.

Thus, to the extent claim 1 requires the presence of stem cells, in its broadest sense, claim 1 only requires the presence of two stem cells, which can be any combination of PHSCs, S-cells and/or CFU-S cells.[10] The examiner, patent owner and patent owner's declarants have not taken this embodiment into account in arguing for and against the patentability of claim 1 in view of the disclosure of Shope.

Patent owner is correct in arguing that Shope does not discuss the presence of stem cells in the cryopreserved mononuclear cord blood fraction. On the other hand, Shope does not discuss the absence of such cells in that fraction. Rather, the reference is silent on the point. Under these circumstances, our appellate reviewing court has made it clear that it is applicant's, here patent owner's, burden to establish that the respective products differ in a manner beyond a mere difference in properties. In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition."

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[10] The examiner's finding at page 13 of the Examiner's Answer that "plurality" as used in this case should be interpreted to mean "as little as 6%" finds no support in the specification of the '681 patent and, thus, is clearly erroneous.

(Citations omitted)). Patent owner's burden under the circumstances presented herein was described in In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) (footnote omitted) as follows:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on `inherency' under 35 U.S.C. § 102, on `prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

Here, one embodiment of the '681 patent which is encompassed by claim 1 of the patent involves a separated mononuclear cell fraction containing a plurality of stem cells. See column 37, lines 65-66, ("Cell separation procedures can be used if desired."). Both the specification of the '681 patent and Shope form mononuclear cell fractions from cord blood in the same manner. In fact, both describe the separation procedure used to prepare the cord blood examples disclosed in the respective disclosures in the same terse manner. Compare column 34, line 50-column 37, line 58, and Table II of the '681 patent ("separation with Ficoll-Hypaque") with the bridging paragraph of page 326 of Shope ("separated in a Ficoll-hypaque gradient"). While the specification of the '681

patent provides a detailed protocol for separating "samples of bone marrow or peripheral blood" using Ficoll-Hypaque separation in section 6.3.1, there is no evidence that any of the mononuclear cell fractions identified in Table III of the '681 patent were actually prepared using this protocol. Thus, the specification of the '681 patent parallels the disclosure of Shope in that one attempting to recreate the specific cord blood fractions described in the respective disclosures would have to resort to extrinsic disclosures such as the Boyum reference[11] cited in Shope or section 6.3.1 of the specification of the '681 patent. Patent owner's argument at page 72 of the Appeal Brief that "one cannot reasonably reproduce the method disclosed in Shope" is unavailing and does not serve as a proper basis to avoid patent owner's burden under Best.

A similar situation exists in regard to the discussion on this record surrounding the effect Ende has on the patentability of the claims on appeal. The examiner has apparently interpreted claim 1 on appeal as requiring the presence of an exogenous cryopreservative. This is seen in that the rejection proposed by the examiner is premised on the examiner's determination that "it would have been obvious to one of ordinary skill in the art to

[11] Boyum, A., Scand. J. Clin. Lab. Invest., 21 (Suppl 97:77) (1968). Boyum appears to be the discoverer of the separation technique which is referred to throughout the prior art as "Ficoll-Hypaque" or variants thereof.

substitute the umbilical cord blood, as taught by Ende et al., for the peripheral blood, fetal liver, or bone marrow in the composition, which additionally comprises DMSO, as taught by Löwenberg and Moretti et al." (paragraph bridging pages 7-8 of the Examiner's Answer).

However, it is not apparent to us that claim 1 requires an exogenous cryopreservative. Note that claim 1 only requires the presence of a "cryopreservative" but does not require that the "cryopreservative" be present in any specific amount, either functionally or through use of finite limits. As stated in In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963), "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same." Here, the specification of the '681 patent acknowledges that albumin, a protein that is normally present in blood, can function as a cryopreservative. See column 22, line 46. Thus, human blood, including cord blood, contains a compound that possesses cryopreservative properties. Whether albumin will function as a cryopreservative under a given set of circumstances will no doubt depend upon such factors as the nature of the composition to be frozen, the amount of albumin present etc. Whether albumin will function as a cryopreservative in a given set of circumstances is a separate inquiry apart from whether it possesses the property of being a "cryopreservative." Since claim 1 only requires the presence of an undefined amount of

a compound which possesses the property of being a cryopreservative, it appears that claim 1 can reasonably be interpreted to read upon fresh whole human cord blood.

Less this be considered a strained interpretation of claim 1, we make reference to sections 6.11.1-6.11.4 of the specification of the '681 patent where whole murine fetal blood, which did not contain an exogenous cryopreservative agent, was used to reconstitute the hematopoietic system of lethally irradiated mice. Note also that patent owner relies upon Pollack[12] as evidence of non-obviousness which states in the abstract that "Cord blood from compatible donors can be harvested at birth and used immediately or frozen for subsequent use in hematopoietic reconstitution." Thus, the record supports interpreting claim 1 as reading on whole cord blood that does not contain an exogenous cryopreservative.

Apart from not recognizing or acknowledging the full scope of claim 1 on appeal, patent owner did not take into account the correct legal standards in responding to the rejections based on Ende. For example, patent owner states at page 119 of the Appeal Brief that knowledge gleaned from Ende that "cord blood can be used in a transfusion to

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[12] Pollack et al. (Pollack), "DNA Amplification for DQ Typing as an Adjunct to Serological Prenatal HLA Typing for the Identification of Potential Donors for Umbilical Cord Blood Transplantation," Human Immunology, 30, 45-9 (1991).

supply red blood cells . . . sheds no light on the presence, much less potential utility of any long-term marrow repopulating cord blood stem cells, nor does it support any motivation to freeze human neonatal/fetal blood. . . ."[13] Patent owner goes on to argue at page 119 of the Appeal Brief that none of the references used in these rejections, either alone or in combination, would have led "one of ordinary skill in the art to a reasonable expectation that human neonatal or fetal blood contains long-term marrow repopulating stem cells so as to provide utility for hematopoietic reconstitution."

These arguments presuppose that the prior art relied upon in a rejection under 35 U.S.C. § 103 must suggest the same purpose which formed the basis of the claimed invention under review. This is not the case. As set forth in In re Kemps, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996), citing In re Dillon, 919 F.2d 688, 693, 16 USPQ2d 1897,1901 (Fed. Cir. 1990)(in banc) all that is needed is that the prior art suggest the claimed invention for any reason. Thus, that Ende observed only a temporary improvement in the patient's condition does not disable Ende as prior art.

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[13] Patent owner's questioning of whether whole cord blood contains stem cells is not understood in light of the numerous citations listed above, some of which were authored or co-authored by the present inventors, which establish that, regardless of how the term is defined, whole human cord blood contains stem cells.

Furthermore, patent owner's arguments in regard to the rejections based upon Ende take an overly narrow view of the term "stem cell" in that they are cast in the context that Ende must suggest the presence of stem cells which provide long term hematopoietic reconstitution which patent owner is urging are PHSCs, not S-cells or CFU-S cells. As set forth above, the specification of the '681 patent acknowledges that whole cord blood contains S-cells as determined and defined by Nakahata (J. Clin. Invest.).

The narrow view that patent owner and the examiner have taken of the claims on appeal also affects how the evidence of non-obviousness relied upon by patent owner is viewed. As set forth in In re Tiffin, 448 F.2d 791, 792, 171 USPQ 294, 294 (CCPA 1971), evidence of secondary considerations such as commercial success and long-felt need must be commensurate in scope with the claims under review. These issues have not been properly considered by patent owner and the examiner.

B

1. Shope

Shope and Koike are similar in that both describe separating whole cord blood using the Ficoll-Hypaque technique and cryopreserving the resulting mononuclear cell fraction. Koike appears to be significantly more relevant in determining the patentability of

the claims on appeal than Shope since Koike demonstrated that the thawed cryopreserved mononuclear fraction obtained from cord blood contained viable progenitor cells. Of most importance is Koike's statement that in view of the findings reported in the reference and the known fact that cord blood contains many pluripotent and nearby progenitor cells "comparable to marrow cells," fetal hematopoietic cells may be useful as a source of hematopoietic progenitor cells for marrow transplantation, i.e., reconstituting the hematopoietic system.

One of the embodiments encompassed by claim 1 of the '681 patent is a composition obtained by separating whole cord blood using a Ficoll-Hypaque technique and cryopreserving the mononuclear fraction. Section 6.7 of the '681 patent reports results obtained when cryopreserved mononuclear fractions were thawed and assayed for progenitor viability. Like Koike, the '681 patent reports that the thawed fractions contained viable progenitor cells. Shope, unlike Koike and the '681 patent, does not discuss the presence or absence of progenitor cells in the mononuclear fractions obtained in that reference, either before or after cryopreservation. Shope simply was not interested in that aspect of the separated fraction. That does not mean that the separated mononuclear fractions of Shope did not contain progenitor cells, or for that matter, stem cells. It only

means that Shope's interests in investigating this fraction of cord blood were divergent from the present inventors and Koike.

In any event, patent owner and the examiner have considered Shope in a vacuum, apart from the disclosure of the '681 patent and the prior art discussed above. For example, one of the issues presented in this appeal by the examiner and patent owner concerns the manner in which Shope separated the whole cord blood and obtained the mononuclear fraction and whether Shope can be considered an enabling reference. Patent owner argues that Shope is vague and contains deficiencies as to the separation procedure used to obtain the mononuclear fraction relied upon by the examiner. See the Appeal Brief, pages 69-73. In response, the examiner takes the position that Shope's citation of Boyum for this aspect of the described procedure amounts to an "incorporation of the reference in its entirety." See pages 15-16 of the Examiner's Answer. In our view, this issue amounts to much ado about nothing.

First, we would agree with patent owner that Shope does not provide details of how the mononuclear fractions described in that reference were obtained. We disagree with the examiner that Shope's citation of Boyum means that the details described in that reference were necessarily used. However, the point which patent owner misses in taking this position is that the disclosure of the '681 patent lacks the same details in its

description of the mononuclear fractions obtained using "Ficoll-Hypaque." While patent owner makes much of the detailed description of the separation procedure which appears in section 6.3.1 of the '681 patent (Appeal Brief, pages 70-71), that protocol is stated to be used for bone marrow and peripheral blood, not cord blood.[14] The '681 patent, in setting forth progenitor cell assay results for separated mononuclear fractions in Table III, only states that those fractions were obtained using Ficoll-Hypaque. Thus, the '681 patent provides as much detail in this respect as Shope.[15]

Second, patent owner and the examiner have not taken the scope of the claims on appeal into account in their consideration of this issue. Until it is determined what a "stem cell" is and what constitutes a "plurality" according to the claims on appeal, it is futile to try

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[14] If this means that the detailed procedure set forth in this section of the '681 was used in a prior art sense to separate bone marrow and peripheral blood to obtain fractions enriched in stem and/or progenitor cells, patent owner should acknowledge as much and ensure that such prior art is of record and brought to the examiner's attention.

[15] To the extent that patent owner would continue to urge that a mononuclear fraction of whole cord blood obtained by "Ficoll-Hypaque" will not necessarily contain a "plurality of stem cells," i.e., references such as Shope are non-enabling in this respect, the same question of enablement arises in respect to the present claims since they are inclusive of embodiments in which the plurality of stem cells are obtained by fractionating cord blood using "Ficoll-Hypaque." We recognize that questions of enablement which affect unamended patent claims can not be raised in a reexamination. Thus, patent owner should consider filing a reissue application to have these issues considered if this position is maintained. 37 CFR § 1.552(c).

to determine whether Shope, or for that matter, any reference adversely affects the patentability of the claims on appeal. See In re Steele, 305 F.2d 859, 863, 134 USPQ 292, 295 (CCPA 1962).

Third, and perhaps most importantly, the discussion of this issue by patent owner and the examiner ignores the fact that Nakahata (J. Clin. Invest.), acknowledged by the '681 patent as describing the S-cell stem cell which is within the claims on appeal, provides even less detail as to how the mononuclear fractions used in that work were obtained. Nakahata (J. Clin. Invest.) only states (page 1324) that mononuclear cells isolated from umbilical cord blood were cultured. Despite this lack of procedural detail, Nakahata (J. Clin. Invest.) is consistently credited in the prior art, the '681 patent, and publications subsequent to the filing date of the '681 patent as discovering the S-cell without a hint that one would not be able to reproduce that work. It is curious that patent owner would advance this position when the '681 patent itself and publications authored and co-authored by the present inventors credit Nakahata (J. Clin. Invest.) in this regard.

On its face, Koike is more relevant in determining the patentability of the claims on appeal than Shope since it involves hematopoietic progenitor cells and directly suggests the use of appropriate cord blood fractions in reconstituting the hematopoietic system. Koike describes compositions which appear to be identical or substantially identical to

compositions described in the specification of the ‘681 patent and encompassed by the claims on appeal. If so, as set forth above, it is appropriate to shift the burden to patent owner to establish that cord blood fractions separated as described in Koike would not necessarily contain “a plurality of viable human neonatal or fetal hematopoietic stem cells” (“inherency” under 35 U.S.C. § 102) or that one of ordinary skill in the art would not reasonably expect that such cord blood fractions contain a plurality of those cells (“prima facie obviousness” under 35 U.S.C. § 103). In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

This is not to say that the claims on appeal are patentable or unpatentable over Shope. Rather, we do not find it appropriate to expend the resources of this board to make the findings and provide the analysis needed in order to reach a final decision on the patentability of the claims on appeal on the basis of Shope on this record. The prosecution and examination of this reexamination have not been premised on a clear and consistent interpretation of the claims on appeal. As a result, relevant judicial precedent has not been properly considered and applied. The lack of a proper interpretation of the claims has also resulted in relevant prior art such as Koike, Nakahata (J. Clin. Invest.), and the Vidal thesis being overlooked, withdrawn, or ignored by both patent owner and the

examiner. Under these circumstances, we will not proceed to decide the rejection based on Shope. Rather, we vacate the rejection under 35 U.S.C. § 103 based on Shope.

2. Rejections based on Ende

We reach the same conclusion in regard to the rejections based in part upon Ende. Absent the issues raised in these rejections being based upon a definitive interpretation of the claims on appeal, we do not find it appropriate to spend the resources of this board in making de novo findings which should be made by the examiner and/or the patent owner in the first instance. Accordingly, we vacate the rejections premised upon Ende.

REMAND

1. Claim interpretation

In deciding patentability issues under 35 U.S. C. § 103, the court observed in Panduit Corp. v. Dennison Manufacturing Co., 810 F.2d 1561, 1567-68, 1 USPQ2d 1593, 1597 (Fed. Cir.), cert. denied, 481 U.S. 1052 (1987), "Analysis begins with a key legal question--what is the invention claimed?" since "[c]laim interpretation . . . will normally control the remainder of the decisional process." Claims under review in a reexamination are given their broadest reasonable interpretation, consistent with the specification. In re Paulsen, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994). Patent owner must not engage "in a post hoc attempt to redefine the claimed invention by impermissibly incorporating language appearing in the specification into the claims." Id.

Upon return of the file, the examiner should initially review each claim pending in this reexamination and determine its scope, using appropriate legal standards for ex parte examination. The record should reflect in what manner the examiner has interpreted the claims and, thus, on what basis the patentability of the claims has been determined. The facts in Genentech, Inc. v. Wellcome Foundation Ltd., 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994) serve as an example of the difficulties which can arise when a patent issues and the record does not reflect how the examiner interpreted the claims and

determined patentability There, a phrase used in the claims, tissue plasminogen activator, was defined in four different ways in the specification. Genentech, at 1563, 31 USPQ2d at 1167. The court observed that "[t]hese diverse definitions reflect either inartful drafting, a conscious attempt to create ambiguity about the scope of the claims, or a desire to claim a wide variety of materials not described or enabled in the specification," Genentech, at 1564, 31 USPQ 2d at 1167. The court resolved that situation by avoiding "those definitions upon which the PTO could not reasonably have relied when it issued the patent." Id. This was seen to be appropriate because it avoided "the possibility of an applicant obtaining in court a scope of protection which encompasses subject matter that, through the conscious efforts of the applicant, the PTO did not examine." Id. (footnote omitted). Here, the examiner has yet another opportunity to create a record which will indicate to those who follow on what basis the claims pending in this reexamination were determined to be patentable or unpatentable. To aid in focussing these efforts, we make the following observations.

The examiner should define the scope the term "stem cell" as it is used in the claims. As set forth above, it appears that patent owner wants the claims to be read as requiring the presence of a stem cell which is pluripotential and possesses "long-term marrow-repopulating" properties. On that basis, patent owner would distinguish this type

of stem cell from the CFU-S stem cell and the S-cell stem cell. However claim 1 of the '681 patent only calls for a "stem cell" without qualification. Claim 6 appears to be directed to the S-cell[16] while claim 7 appears to be directed to CFU-S. Claim 9 is concerned with stem cells "characterized by the ability to reconstitute the hematopoietic system of a host into which it is introduced." Noticeably missing from this language is the qualifying phrase "long-term" which has played a prominent role in the manner in which patent owner has urged patentability.

A second aspect of the claims which warrants specific attention is the word "plurality." As indicated above, it appears that the original examiner interpreted this aspect of the claimed subject matter in a restrictive manner which may be unwarranted on this record.

A third claim term which the examiner should pay special attention to is the word "cryopreservative." It appears that the examiner has read the claims as requiring the presence of an exogenous compound which possesses this property. For the reasons

[16] The presence of claim 7 belies the original examiner's holding, from which she later distanced herself, that the claims on appeal do not include the S-cell described by Nakahata (J. Clin. Invest.).

explained above, this may also be an undue narrowing of the claim. Albumin, a component of cord blood, is admitted by patent owner to possess cryopreservative properties.

2. Patentability issues

Having determined the scope of the claims on appeal, the examiner will then be in a proper position to determine their patentability. We make the following comments in an attempt to focus future proceedings.[17]

A. Whole cord blood

1. If it is determined that the requirement in claim 1 of a "cryopreservative" can reasonably[18] be interpreted to include any compound which has that function, e.g., albumin, the examiner should consider whether references which describe whole cord blood anticipate claims such as claim 1. If such a rejection is instituted by the examiner, in order to avoid conflict with the above-noted holding in Portola, the examiner

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[17] It was determined in In re Portola Packaging Inc., 110 F.3d 786, 791, 42 USPQ2d 1295, 1300 (Fed. Cir. 1997) that substantial new grounds of patentability in reexamination can only rest on prior art that was not before the examiner in an earlier examination.

[18] The examiner should keep in mind that, absent a clear definition in the specification, the fact that patent owner might be able to point to a definition or usage of a word or phrase that conforms to its interpretation does not make the PTO's interpretation unreasonable. In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1029 (Fed. Cir. 1997). Also it is patent owner's burden to precisely define the invention, not the PTO's. Id.

should not rely upon references considered in the examination of the '681 patent such as Ende. Rather, references such as Koike and the Vidal thesis which are new to this reexamination, or other prior art describing whole cord blood not considered in the examination of the '681 patent should be applied.

2. If the claims are amended to clearly require the presence of an exogenous cryopreservative, the examiner should consider the following. Long before the present invention, researchers were using cord blood in any number of studies. See the references discussed in the Background section of this opinion. It should not be disputed that freshly harvested whole human cord blood contains a plurality of human stem cells. If the prior art would have suggested cryopreserving whole cord blood for any reason[19] by use of an exogenous cryopreservative, the subject matter of claims such as claim 1 might be unpatentable under 35 U.S.C. § 103 for that reason. Thus, references such as Shope, Radvany and Koike, which establish that it was known prior to the present invention that cryopreserved cord blood fractions contained viable cells upon thawing, may have suggested to one of ordinary skill in the art to cryopreserve whole cord blood to store it for

[19] The examiner should also keep in mind, as set forth above, that the so-called motivation to combine references does not have to be identical to patent owner's to establish obviousness. In re Kemps, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996).

uses other than hematopoietic reconstitution, e.g., to study other properties of cord blood. A suggestion to cryopreserve whole cord blood using an exogenous cryopreservative may be found if it would have been reasonable to find that researchers interested in studying the properties of whole cord blood, or fractions thereof, may not be conveniently located to hospitals where fresh cord blood is conventionally collected or if such researchers can not immediately use the freshly harvested cord blood. Those circumstances may provide the requisite suggestion, reason or motivation[20] to cryopreserve whole cord blood.

[20] As stated in Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629, (Fed. Cir. 1996) (citation omitted):

> It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references.

B. Cord blood fractions

As discussed above, the claims on appeal read on cord blood fractions which contain the specified stem cells and a cryopreservative. After determining on the record the scope of the terms used in the claims such as “stem cell” and “plurality,” the examiner should carefully consider the various prior art cord blood fractions.

1. Koike

Obviously the examiner should pay careful attention to Koike since it describes cryopreserved cord blood fractions which appear to be the same or substantially the same as those described and presumably claimed in the ‘681 patent. The cord blood fractions described in Koike were prepared by the same or substantially the same methods described in the ‘681 patent. These facts may reasonably shift the burden of going forward to patent owner to establish that cord blood fractions prepared according to Koike differ in a patentably distinct manner from those encompassed by the claims on appeal. In re Best, 562 F.2d 1252, 1255, 26 USPQ 430, 433 (CCPA 1977).

2. Nakahata (J. Clin. Invest.)

Apart from Koike itself being pertinent prior art, the examiner should consider Nakahata (J. Clin. Invest.) in light of Koike and/or the Vidal thesis.[21] Koike and the Vidal thesis indicate that cord blood fractions separated by Ficoll-Hypaque would be useful in the restoration of the hematopoietic system of humans. Since Nakahata (J. Clin. Invest.) describes cord blood fractions which contain a plurality of stem cells as defined in the specification of the '681 patent and included within the claims thereof, see, e.g., claim 6, it would further appear that Koike and/or the Vidal thesis would have provided the requisite reason, suggestion or motivation to cryopreserve the Nakahata (J. Clin. Invest.) cord blood fractions for the purpose of hematopoietic reconstitution.

[21] It was also determined in In re Portola Packaging Inc., 110 F.3d 786, 790, 42 USPQ2d 1295, 1299 (Fed. Cir. 1997), that a presumption exists that the examiner considers a cited reference, not only by itself, but in combination with "all other cited references." It is not clear from this record that Koike and the Vidal thesis were properly considered individually, let alone in combination with "all other cited references."

3. Leary, Civin, Koike and the Vidal thesis

The '681 patent indicates at columns 21, lines 60-68, that Leary describes procedures through which cord blood fractions enriched in hematopoietic stem cells and progenitor cells may be obtained. The procedures described in Leary involve the separation of single cells from mononuclear fractions of cord blood[22] through use of a monoclonal antibody (Mab) identified as My-10. The single cells were replated and multi-lineage colonies were subsequently observed. Leary concluded that the data obtained were consistent with the stochastic principle of stem cell differentiation.

Civin used Mab My-10 to form a cell suspension of cells consisting essentially of cells which express the My-10 antigen and are capable of restoring the production of lymphoid and hematopoietic cells to a human patient (column 7, line 65-column 8, line 9). Civin also explicitly suggests (column 7, lines 38-42) that the cell suspensions of that reference which are capable of reconstituting the lymphoid and hematopoietic system be cryopreserved. Civin is broadly directed to a "cell suspension prepared from human tissue containing cells (i.e., marrow or blood cells)" (column 6, lines 37-50) but does not explicitly

[22] As indicated in the "methods" section of Leary, the mononuclear fractions were obtained by using "Ficoll-Paque."

teach that human cord blood is a “human tissue” from which the cell suspensions of that reference may be obtained. But see Leary in this regard.

The examiner should determine whether one of ordinary skill in the art at the time of the filing date of the ‘681 patent would have found it obvious from a consideration of Leary and Civin together to use Mab My-10 to form a cell suspension from human cord blood containing stem cells and progenitor cells in amounts such that the cell suspension would be useful in reconstituting the lymphoid and hematopoietic systems of humans. The reconstitution of the hematopoietic system taught by Civin appears to be of the “long-term” variety vigorously argued by patent owner to have been unobvious at the time of the present invention.

Koike and the Vidal thesis each suggests the cryopreservation of appropriate cord blood fractions for the purpose of hematopoietic reconstitution. Importantly, the Vidal thesis recognizes that due to the immuno-tolerance of the newborn, cord blood from non-HLA donors should be useful in transplantations. These are all facts which patent owner urges are missing from Shope and Ende.

Upon return of the file, the examiner should carefully consider whether these teachings combined[23] would have rendered the subject matter of the claims on appeal unpatentable under 35 U.S.C. § 103.

C. Evidence of non-obviousness

If patent owner relies upon evidence of non-obviousness in future proceedings, the examiner should take care to ensure that the evidence is evaluated in the proper legal context. As explained above, evidence of commercial success and long-felt need must be commensurate in scope with the pending claims. This is but another reason why claim interpretation plays a pivotal role in determining patentability and should be the first step an examiner performs in the examination.

Furthermore, evidence based upon a so-called long-felt need must be evaluated in the context of the prior art.[24] Viewing the successful hematopoietic reconstitutions by use

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[23] A rejection based solely upon Civin and Leary, which may be legally sufficient under 35 U.S.C. § 103 to establish the unpatentability of the claims, may not be proper in this reexamination in light of Portola. However, Koike and the Vidal thesis add valuable facts in addition to those gleaned from Civin and Leary. A rejection based upon all four references, if found to be appropriate by the examiner, would appear to be procedurally proper under Portola.

[24] The court in Newell Companies, Inc. v. Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426, (Fed. Cir. 1988) observed that once the prior art supplied a "key element" of an invention, there was no longer a long-felt need or problem to be solved.

(continued...)

of cord blood or cord blood fractions documented by patent owner in light of the teachings of Koike, the Vidal thesis, Civin, Leary and Nakahata (J. Clin. Invest.) presents the person of ordinary skill in the art a completely different picture than when those successes are viewed in the relative darkness of Shope. Even viewing the relatively limited success of Ende in light of the knowledge gained from the prior art work of Koike, the Vidal thesis, Civin, Leary and Nakahata (J. Clin. Invest.) the person of ordinary skill in the art would have had a substantially different picture. Indeed, Golde and Broxmeyer (1991) put the present invention in perspective when stating that the prior art understood that cord blood contained stem cells prior to the present invention and that the present inventors only put this prior art knowledge to work in "suggesting" that cord blood might be useful for the purpose of restoring the hematopoietic system. However, Koike, Civin, Leary, and the Vidal thesis also "suggested" this use. Precisely how the claims on appeal distinguish over this prior art teaching is not clear to this panel.

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[24](...continued)
After the disclosures of Koike, the Vidal thesis, Civin, Leary and Nakahata (J. Clin. Invest.) were placed in the prior art, it is not clear what long-felt need or problem remained to be solved. In relevant part, the disclosure and claims of the '681 patent appear to be co-extensive with the prior art so it is not clear what "long-felt" need the claimed invention satisfies.

This application, by virtue of its “special” status, requires an immediate action. MPEP § 708.01(d). It is important that the Board be informed promptly of any action affecting the appeal in this case.

VACATED; REMANDED

William F. Smith Administrative Patent Judge	)	
Teddy S. Gron Administrative Patent Judge	)	BOARD OF PATENT APPEALS AND INTERFERENCES
Elizabeth C. Weimar Administrative Patent Judge	)	

Appeal No. 96-2079
Reexamination Control No. 90/003182

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